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(71) Applicant: WYETH [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).

(72) Inventors: LI, Yanfang; 3 Woodlane Road, Lawrenceville, NJ 08648 (US). ZHOU, Ping; 28 Marion Drive, Plainsboro, NJ 08536 (US).

(74) Agents: BERG, Egon, E.; Wyeth, Patent Law Department, Five Giralda Farms, Madison, NJ 07940 et al. (US).

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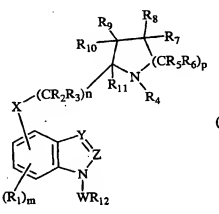
(54) Title: HETEROCYCLYLALKOXY-, -ALKYLTHIO- AND -ALKYLAMINOBENZAZOLE DERIVATIVES AS 5-HYDROXYTRYPTAMINE-6 LIGANDS

(57) Abstract: The present invention provides a compound of formula I and the use thereof for the therapeutic treatment of disorders relating to or affected by the 5-HT6 receptor.



(I)

WO 02/085853 A2

HETEROCYCLYLALKOXY-, -ALKYLTHIO- AND -ALKYLAMINOBENZAZOLE DERIVATIVES AS 5-HYDROXYTRYPTAMINE-6 LIGANDS

This invention relates to heterocyclylalkoxy-, -alkylthio- and -alkylaminobenzazole derivatives as 5-hydroxytryptamine-6 ligands, to processes for preparing them, to methods of using them and to pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Various central nervous system disorders such as anxiety, depression, motor disorders, etc., are believed to involve a disturbance of the neurotransmitter 5-hydroxytryptamine (5-HT) or serotonin. Serotonin is localized in the central and peripheral nervous systems and is known to affect many types of conditions including psychiatric disorders, motor activity, feeding behavior, sexual activity, and neuroendocrine regulation among others. The effects of serotonin are regulated by the various 5-HT receptor subtypes. Known 5-HT receptors include the 5-HT1 family (e.g. 5-HT1A), the 5-HT2 family (e.g. 5-HT2A), 5-HT3, 5-HT4, 5-HT5, 5-HT6 and 5-HT7 subtypes.

The recently identified human 5-hydroxytryptamine-6 (5-HT6) receptor subtype has been cloned, and the extensive distribution of its mRNA has been reported. Highest levels of 5-HT6 receptor mRNA have been observed in the olfactory tubercle, the striatum, nucleus accumbens, dentate gyrus and CA1, CA2 and CA3 regions of

the hippocampus. Lower levels of 5-HT6 receptor mRNA were seen in the granular layer of the cerebellum, several diencephalic nuclei, amygdala and in the cortex. Northern blots have revealed that 5-HT6 receptor mRNA appears to be exclusively present in the brain, with little evidence for its presence in peripheral tissues. The high affinity of a number of antipsychotic agents for the 5-HT6 receptor, in addition to its mRNA localization *in striatum*, olfactory tubercle and nucleus accumbens suggests that some of the clinical actions of these compounds may be mediated through this receptor. Therefore, 5-HT6 receptor ligands are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, attention deficit disorder, migraine, cognitive memory enhancement (e.g. for the treatment of Alzheimer's disease), sleep disorders, feeding disorders (e.g. anorexia and bulimia), panic attacks, withdrawal from drug abuse (e.g. cocaine, ethanol, nicotine and benzodiazepines), schizophrenia, or the like; or in the treatment of certain gastrointestinal disorders such as irritable bowel syndrome.

Therefore, it is an object of this invention to provide compounds which are useful as therapeutic agents in the treatment of a variety of central nervous system disorders related to or affected by the 5-HT6 receptor.

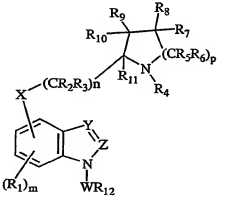
It is another object of this invention to provide therapeutic methods and pharmaceutical compositions useful for the treatment of central nervous system disorders related to or affected by the 5-HT6 receptor.

It is a feature of this invention that the compounds provided may also be used to further study and elucidate the 5-HT6 receptor.

These and other objects and features of the invention will become more apparent by the detailed description set forth hereinbelow.

SUMMARY OF THE INVENTION

The present invention provides a compound of formula I



(I)

wherein

W is SO_2, CO, CONH, CSNH or $(CH_2)_x$;

X is O, SO_y or NR_{13};

Y is CR_{14} or N;

Z is CR_{15} or N with the proviso that when Y is N then Z must be CR_{15};

m and x are each independently 0 or an integer of 1, 2 or 3;

n and p are each independently an integer of 1, 2 or 3;

R_1 is halogen, CN, OR_{16}, CO_2R_{17}, $CONR_{18}R_{19}$, $CNR_{20}NR_{21}R_{22}$, $SO_2NR_{23}R_{24}$, SO_wR_{25}, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_4 is H, $CNR_{25}NR_{27}R_{28}$ or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{12} is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

y and w are each 0 or an integer of 1 or 2;

R_{13} is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{14} and R_{15} are each independently H, halogen or a C_1-C_6alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_{16} is H, COR_{29} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{17} and R_{29} are each independently H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26}, R_{27} and R_{28} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{23} and R_{24} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{25} is an optionally substituted C_1-C_6alkyl, aryl, or heteroaryl group; or

the stereoisomers thereof or the pharmaceutically acceptable salts thereof.

The present invention also provides methods and compositions useful for the therapeutic treatment of

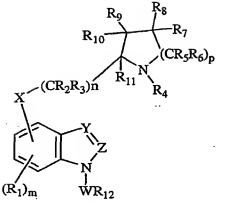
central nervous system disorders related to or affected by the 5-HT6 receptor.

The present invention further provides a method for the preparation of compounds of formula I and a compound useful therefor.

DETAILED DESCRIPTION OF THE INVENTION

The 5-hydroxytryptamine-6 (5-HT6) receptor is one of the most recent receptors to be identified by molecular cloning. Its ability to bind a wide range of therapeutic compounds used in psychiatry, coupled with its intriguing distribution in the brain has stimulated significant interest in new compounds which are capable of interacting with or affecting said receptor. At present, there are no known fully selective agonists. Significant efforts are being made to understand the possible role of the 5-HT6 receptor in psychiatry, cognitive dysfunction, motor function and control, memory, mood and the like. To that end, compounds which demonstrate a binding affinity for the 5-HT6 receptor are earnestly sought both as an aid in the study of the 5-HT6 receptor and as potential therapeutic agents in the treatment of central nervous system disorders.

Surprisingly, it has now been found that heterocyclylalkoxy-, -thioxy- or -aminobenzazole derivatives of formula I demonstrate 5-HT6 affinity. Advantageously, said benzazole derivatives may be used as effective therapeutic agents for the treatment of central nervous system (CNS) disorders associated with or affected by the 5-HT6 receptor. Accordingly, the present invention provides heterocyclylalkoxy-, -alkylthio- or -alkylaminobenzazole derivatives of formula I



(I)

wherein

W is SO_2, CO, CONH, CSNH or $(CH_2)_x$;

X is O, SO_y or NR_{13};

Y is CR_{14} or N;

Z is CR_{15} or N with the proviso that when Y is N then Z must be CR_{15};

m and x are each independently 0 or an integer of 1, 2 or 3;

n and p are each independently an integer of 1, 2 or 3;

R_1 is halogen, CN, OR_{16}, CO_2R_{17}, $CONR_{18}R_{19}$, $CNR_{20}NR_{21}R_{22}$, $SO_2NR_{23}R_{24}$, SO_yR_{25}, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_4 is H, $CNR_{26}NR_{27}R_{28}$ or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{12} is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

y and w are each 0 or an integer of 1 or 2;

R_{13} is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{14} and R_{15} are each independently H, halogen or a C_1-C_6alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_{16} is H, COR_{29} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{17} and R_{29} are each independently H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

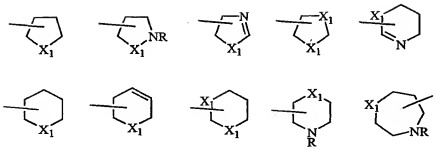
R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26}, R_{27} and R_{28} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{23} and R_{24} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{25} is an optionally substituted C_1-C_6alkyl, aryl, or heteroaryl group; or

the stereoisomers thereof or the pharmaceutically acceptable salts thereof.

As used in the specification and claims, the term halogen designates Br, Cl, I or F and the term cycloheteroalkyl designates a C_5-C_7cycloalkyl ring system containing 1 or 2 heteroatoms, which may be the same or different, selected from N, O or S and optionally containing one double bond. Exemplary of the cycloheteroalkyl ring systems included in the term as designated herein are the following rings wherein X_1 is NR, O or S and R is an optional substituent as described hereinbelow.



Similarly, as used in the specification and claims, the term heteroaryl designates a 5- to 10-membered aromatic ring system containing 1, 2 or 3 heteroatoms, which may be the same or different, selected from N, O or S. Such heteroaryl ring systems include pyrrolyl, azolyl, oxazolyl, thiazolyl, imidazolyl, furyl, thienyl, quinolinyl, isoquinolinyl, indolinyl, benzothienyl, benzofuranyl, benzisoxazolyl or the like. The term haloalkyl as used herein designates a C_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different and the term haloalkoxy as used herein designates an OC_nH_{2n+1} group having from one to 2n+1 halogen atoms which may be the same or different.

In the specification and claims, when the terms C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C,cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl are designated as being optionally substituted, the substituent groups which are optionally present may be one or more of those customarily employed in the development of pharmaceutical compounds or the modification of such compounds to influence their structure/activity, persistence, absorption, stability or other beneficial property. Specific examples of such substituents include halogen atoms, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio, alkylsuphinyl, alkylsulphonyl, carbamoyl, alkylamido, phenyl, phenoxy, benzyl, benzyloxy,

heterocyclyl (eg heteroaryl or cycloheteroalkyl) or cycloalkyl groups, preferably halogen atoms or lower alkyl groups. Typically, 0-3 substituents may be present. When any of the foregoing substituents represents or contains an alkyl substituent group, this may be linear or branched and may contain up to 12, preferably up to 6, more preferably up to 4 carbon atoms.

Pharmaceutically acceptable salts may be any acid addition salt formed by a compound of formula I and a pharmaceutically acceptable acid such as phosphoric, sulfuric, hydrochloric, hydrobromic, citric, maleic, malonic, mandelic, succinic, fumaric, acetic, lactic, nitric, sulfonic, p-toluene sulfonic, methane sulfonic acid or the like.

Compounds of the invention may exist as one or more stereoisomers. The various stereoisomers include enantiomers, diastereomers, atropisomers and geometric isomers. One skilled in the art will appreciate that one stereoisomer may be more active or may exhibit beneficial effects when enriched relative to the other stereoisomer(s) or when separated from the other stereoisomer(s). Additionally, the skilled artisan knows how to separate, enrich or selectively prepare said stereoisomers. Accordingly, the present invention comprises compounds of Formula I, the stereoisomers thereof and the pharmaceutically acceptable salts thereof. The compounds of the invention may be present as a mixture of stereoisomers, individual stereoisomers, or as an opticaly active form.

Preferred compounds of the invention are those compounds of formula I wherein W is SO_2 or CO. Also preferred are those compounds of formula I wherein X is O. Another group of preferred compounds of the invention are those compounds of formula I wherein Y is CR_{14}. Further preferred compounds of the invention are those

compounds of formula I wherein R_{12} is an aryl or heteroaryl group each optionally substituted; and n is 1.

Examples of R_{12} are aryl e.g., phenyl or naphthyl, or heteroaryl e.g., thienyl (such as thien-2-yl) or quinolyl (such as quinolin-8-yl); said aryl and heteroaryl groups being unsubstituted or optionally substituted by one or more (e.g., 1 to 3) substituents the same or different as described herein. Such substituents include halo, nitro, cyano, thiocyanato, cyanato, hydroxyl, alkyl of 1-6 carbon atoms, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, amino, (C_1-C_6)alkylamino, di-(C_1-C_6alkyl)amino, formyl, (C_1-C_6alkoxy)carbonyl, carboxyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkylthio, (C_1-C_6)alkylsulphinyl, (C_1-C_6)alkylsulphonyl, carbamoyl, (C_1-C_6)alkylamido, phenyl, phenoxy, benzyl, benzyloxy, heteroaryl and cycloheteroalkyl or (C_3-C_8)cycloalkyl groups. Such optionally substituted groups for R_{12} are also examples of aryl or heteroaryl for each of R_1, R_4, R_{13}, R_{14}, R_{15}, R_{16}, R_{17}, R_{23}, R_{24}, R_{25} and R_{29}.

More preferred compounds of the invention are those compounds of formula I having one or more, e.g. all, of the following values: W is SO_2; X is O; and n is 1. Another group of more preferred compounds of the invention are those compounds of formula I having one or more, e.g. all, of the following values: W is SO_2; X is O; Y is CR_{14}; n is 1; and p is 1.

Examples of R_2 and R_3 are hydrogen. An example of m is 0. R_5-R_{11} may all for example be hydrogen.

Among the preferred compounds of the invention are:

1-(phenylsulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;

1-[(5-chlorothien-2-yl)sulfonyl]-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;

1-[(2-fluorophenyl)sulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;

1-[(3-fluorophenyl)sulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;

1-[(4-fluorophenyl)sulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;

1-[(3,4-dimethoxyphenyl)sulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;

4-({4-[2S)-pyrrolidin-2-ylmethoxy]-1H-indole-1-yl}sulfonyl)aniline;

1-(phenylsulfonyl)-4-[(2R)-pyrrolidin-2-ylmethoxy]-1H-indole;

1-(phenylsulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazole;

8-({4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazol-1-yl}sulfonyl)quinoline;

1-[(2-chlorophenyl)sulfonyl]-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazole;

1-[(2-fluorophenyl)sulfonyl]-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazole;

1-[(5-chlorothien-2-yl)sulfonyl]-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazole;

4-({4-[(2S)-pyrrolidin-2-ylmethoxy}-1H-indazol-1-yl}sulfonyl)aniline;

2-chloro-4-({4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazol-1-yl}sulfonyl)aniline;

1-(phenylsulfonyl)-4-(piperidin-2-ylmethoxy)-1H-indole;

4-{[4-(piperidin-2-ylmethoxy)-1H-indol-1-yl]sulfonyl}aniline;

1-[(2-fluorophenyl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indole;

1-[(5-chlorothien-2-yl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indole;

1-[(3-fluorophenyl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indole;

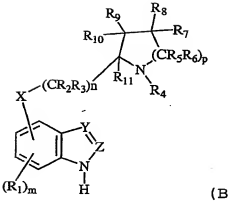
1-[(2-fluorophenyl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indazole;

1-[(2-chlorophenyl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indazole;
1-[(5-chlorothien-2-yl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indazole;
4-(azepan-2-ylmethoxy)-1-(phenylsulfonyl)-1H-indole;
4-{[4-(azepan-2-ylmethoxy)-1H-indol-1-yl]sulfonyl}aniline;
4-(azepan-2-ylmethoxy)-1-[(2-fluorophenyl)sulfonyl]-1H-indole;
4-(azepan-2-ylmethoxy)-1-[(5-chlorothien-2-yl)sulfonyl]-1H-indole;
4-(azepan-2-ylmethoxy)-1-[(3-fluorophenyl)sulfonyl]-1H-indole;
4-(azepan-2-ylmethoxy)-1-[(2-fluorophenyl)sulfonyl]-1H-indazole;
4-(azepan-2-ylmethoxy)-1-[(2-chlorophenyl)sulfonyl]-1H-indazole;
4-(azepan-2-ylmethoxy)-1-[(5-chlorothien-2-yl)sulfonyl]-1H-indazole;
1-(phenylsulfonyl)-5-(pyrrolidin-2-ylmethoxy)-1H-indole;
1-(phenylsulfonyl)-6-(pyrrolidin-2-ylmethoxy)-1H-indole;
1-(phenylsulfonyl)-5-(pyrrolidin-2-ylmethoxy)-1H-indazole;
1-(phenylsulfonyl)-6-(pyrrolidin-2-ylmethoxy)-1H-indazole; or

the stereoisomers thereof or the pharmaceutically acceptable salts thereof.

This invention also provides a process for the preparation of a compound of formula I which comprises one of the following:

a) reacting a compound of formula (B):



(B)

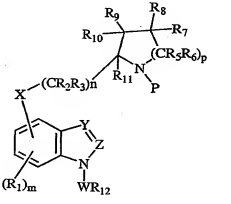
wherein m, n, p, X, Y, Z, R_1, R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are as defined herein, with an appropriate sulphonylating, acylating, carbamoylating, thiocarbamoylating, arylating or alkylating agent containing the group:

$$R_{12}\text{-W-}$$

where R_{12} is as defined above and W is SO_2, CO, CONH, CSNH or $(CH_2)_x$; said reactants protected on reactive sites and/or on reactive substituent groups as required, and removing any protecting groups, to give a corresponding compound of formula (I);

or

b) removing a protecting group from a compound of formula (C)



(I) (C)

wherein m, n, p, W, X, Y, Z, R_1, R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are as defined herein and P is a protecting group to give a compound of formula (I) wherein R_4 is H;

or

c) alkylating a compound of formula (I) as defined in claim 1 wherein R_4 is hydrogen with an alkylating agent of formula R_4-L wherein L is a leaving group, such as halogen, and R_4 is as defined in claim 1 excepting hydrogen to give a corresponding compound of formula (I);

or

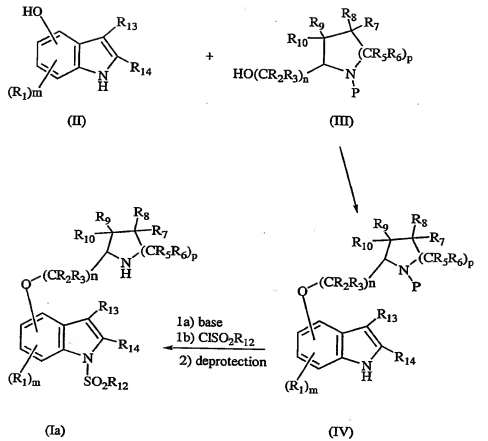
d) converting a compound of formula (I) having a reactive substituent group to a different compound of formula I;

or

e) converting a basic compound of formula (I) to an acid addition salt or vice versa.

Compounds of the invention may be conveniently prepared using conventional synthetic methods and, if required, standard separation and isolation techniques. For example, compounds of formula I wherein W is SO_2; X is O; Y is CR_{13}; Z is CR_{14}; and R_4 and R_{11} are H (Ia) may be prepared by reacting an hydroxyindole of formula II with an N-protected-2-methoxyheterocycle of formula III in the presence of triphenylphosphine and diethyl azodicarboxylate to give the corresponding indol-4-yloxyalkylheterocycle of formula IV. Subsequent sulfonylation and deprotection of the formula IV compound gives the desired formula Ia product. The reaction sequence is illustrated in flow diagram I wherein P represents a protecting group.

Flow Diagram I

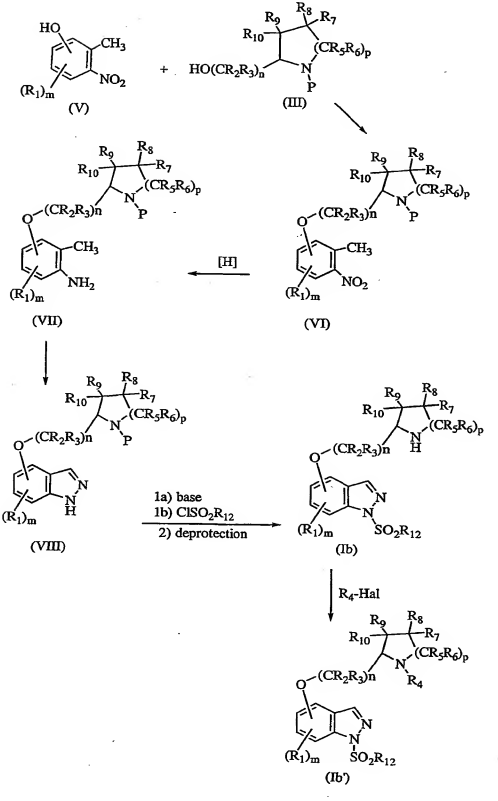


Commonly used protecting groups include t-butyl-carboxylate, benzyl, acetyl, benzyloxycarbonyl, or any conventional group known to protect a basic nitrogen in standard synthetic procedures.

Compounds of formula I wherein W is SO_2; X is O; Y is CH; Z is N and R_4 and R_{11} are H (Ib) may be prepared by reacting a nitromethylphenol of formula V with an N-protected-2-alkoxyheterocyclic compound of formula III in the presence of triphenylphosphine and diethyl azodicarboxylate to give the corresponding heterocyclylalkoxybenzene of formula VI, reducing the nitro group of the formula VI compound, for example via catalytic hydrogenation, to give the amine of formula VII and reacting the formula VII amine with isoamylnitrite in

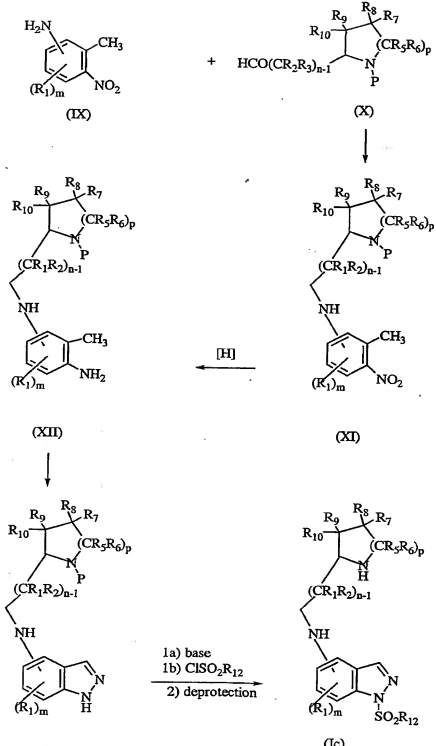
the presence of potassium acetate and acetic anhydride to give the heterocyclyalkoxyindazole of formula VIII. Sulfonylation and deprotection of said formula VIII compound gives the desired compound of formula Ib wherein R_4 is H. Subsequent reaction of the formula Ib compound with a suitable alkylating reagent such as an alkyl or aralkyl halide, R_4-Hal, gives those compounds of formula Ib' wherein R_4 is other than H. The reaction sequence is shown in flow diagram II wherein P is a protecting group and Hal is Cl, Br or I.

Flow Diagram II



Compounds of formula I wherein W is SO_2; X is NH; Y is CH; Z is N; and R_4 and R_{11} are H (Ic) may be prepared by the reductive amination of an N-protected carbonylalkylheterocyclic compound of formula X with a nitromethylaniline compound of formula IX to give the compound of formula XI, reducing the nitro group to give the amine of formula XII and reacting the formula XII amine with isoamylnitrite in the presence of potassium acetate and acetic anhydride to give the heterocyclylalkylamino-indazole of formula XIII. Subsequent sulfonylation and deprotection as described hereinabove give the desired compound of formula Ic. The reaction sequence is shown in flow diagram III.

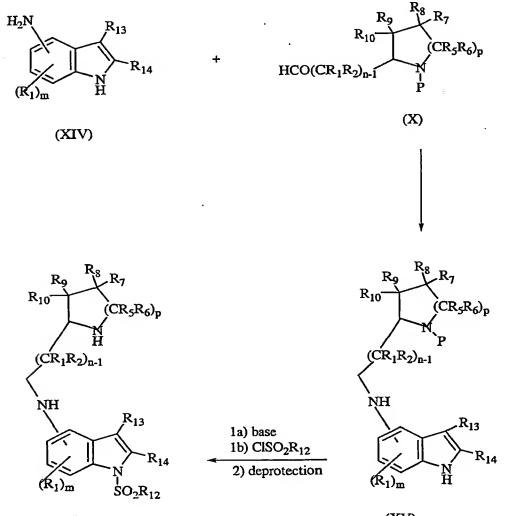
Flow Diagram III



Similarly, compounds of formula I wherein W is SO_2; X is NH; Y is CR_{13}; Z is CR_{14}; and R_4 and R_{11} are H (Id) may be

prepared by the reductive amination of the formula X carboxyaldehyde with an aminoindole of formula XIV to give the compound of formula XV. Subsequent sulfonylation and deprotection gives the desired product of formula Id. The reaction sequence is shown in flow diagram IV.

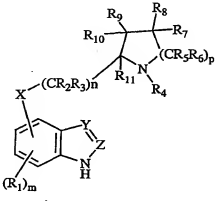
Flow Diagram IV



Compounds of formula I wherein X is S and W is SO_2 may be prepared by employing the appropriate indolylthiol or thiophenol and utilizing the reactions shown in flow diagrams I and II, respectively.

Compounds of formula I wherein W is CO may be prepared by reacting the benzazole precursor, for example a compound of formula IV, VIII, XIII or XV with the appropriate isocyanate, carbonyl halide or carbamoyl halide in the presence of a base. Similarly, compounds of formula I wherein W is $(CH_2)_x$ and x is an integer of 1, 2 or 3 may be prepared by reacting the appropriately substituted alkylhalide with a compound of formula IV, VIII, XIII or XV in the presence of a base. Compounds of formula I wherein W is $(CH_2)_x$ and x is 0 may be prepared via a palladium-catalyzed N-arylation such as that descrited by D. W. Old *et al*, Organic Letters, 2000 (2), pp 1403-1406. Using these and other conventional methods, compounds of formula I may be prepared from readily available starting materials.

Advantageously, the present invention provides a compound of formula XVI

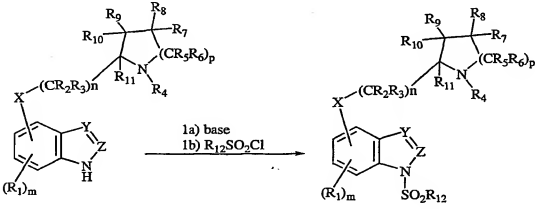


(XVI)

wherein X, Y, Z, m, n, p, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are as defined for formula I. Compounds of formula XVI are useful in the preparation of the therapeutic agents of formula I described hereinabove. Accordingly, the present invention also provides a method

for the preparation of a compound of formula I wherein W is SO_2 (Ie) which comprises reacting a formula XVI compound with a sulfonyl chloride, $R_{12}SO_2Cl$, wherein R_{12} is as defined for formula I in the presence of a base optionally in the presence of a solvent. The reaction is shown in flow diagram V.

Flow Diagram V



(XVI) (Ie)

Bases suitable for use in the method of invention are strong bases such as NaH, KOt-Bu, or any conventional base capable of removing a proton from a basic indole or benzazole nitrogen atom.

Advantageously, the inventive compound of formula I may be utilized in the treatment of central nervous system disorders relating to or affected by the 5-HT6 receptor such as motor, mood, psychiatric, cognitive, neurodegenerative, or the like disorders, for example, Alzheimer's disease, Parkinson's disease, attention deficit disorder, anxiety, epilepsy, depression, obsessive compulsive disorder, migraine, sleep disorders, feeding disorders (such as anorexia or bulimia), schizophrenia, memory loss, disorders associated with

withdrawl from drug abuse, or the like or certain gastrointestinal disorders such as irritable bowel syndrome. Accordingly, the present invention provides a method for the treatment of a disorder of the central nervous system (CNS) related to or affected by the 5-HT6 receptor in a patient in need thereof which comprises providing said patient a therapeutically effective amount of a compound of formula I as described hereinabove. The compounds may be provided by oral or parenteral administration or in any common manner known to be an effective administration of a therapeutic agent to a patient in need thereof.

The therapeutically effective amount provided in the treatment of a specific CNS disorder may vary according to the specific condition(s) being treated, the size, age and response pattern of the patient, the severity of the disorder, the judgment of the attending physician and the like. In general, effective amounts for daily oral administration may be about 0.01 to 1,000 mg/kg, preferably about 0.5 to 500 mg/kg and effective amounts for parenteral administration may be about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg.

In actual practice, the compounds of the invention are provided by administering the compound or a precursor thereof in a solid or liquid form, either neat or in combination with one or more conventional pharmaceutical carriers or excipients. Accordingly, the present invention provides a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an effective amount of a compound of formula I as described hereinabove.

Solid carriers suitable for use in the composition of the invention include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aides,

binders, tablet-disintegrating agents or encapsulating materials. In powders, the carrier may be a finely divided solid which is in admixture with a finely divided compound of formula I. In tablets, the formula I compound may be mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. Said powders and tablets may contain up to 99% by weight of the formula I compound. Solid carriers suitable for use in the composition of the invention include calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, low melting waxes and ion exchange resins.

Any pharmaceutically acceptable liquid carrier suitable for preparing solutions, suspensions, emulsions, syrups and elixirs may be employed in the composition of the invention. Compounds of formula I may be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, or a pharmaceutically acceptable oil or fat, or a mixture thereof. Said liquid composition may contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, coloring agents, viscosity regulators, stabilizers, osmo-regulators, or the like. Examples of liquid carriers suitable for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) or their derivatives, or oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration the carrier

may also be an oily ester such as ethyl oleate or isopropyl myristate.

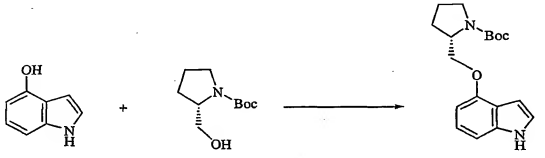
Compositions of the invention which are sterile solutions or suspensions are suitable for intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions may also be administered intravenously. Inventive compositions suitable for oral administration may be in either liquid or solid composition form.

For a more clear understanding, and in order to illustrate the invention more clearly, specific examples thereof are set forth hereinbelow. The following examples are merely illustrative and are not to be understood as limiting the scope and underlying principles of the invention in any way.

Unless otherwise stated, all parts are parts by weight. The term NMR designates nuclear magnetic resonance. The terms THF and EtOAc designate tetrahydrofuran and ethyl acetate, respectively.

EXAMPLE 1

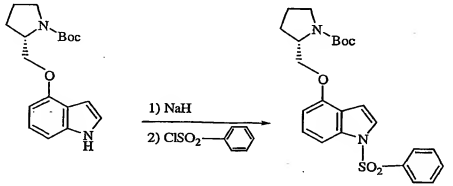
Preparation of t-Butyl (2S)-2-[(1H-indol-4-yloxy)methyl]-1-pyrrolidinecarboxylate



A solution of 4-hydroxyindole (1.33 g, 10.0 mmol), (S)-(-)-1-t-butoxycarbonyl)-2-pyrrolidine methanol (4.02 g, 20.0 mmol) and triphenylphosphine (5.3 g, 20.0 mmol) in THF is treated with diethyl azodicarboxylate (3.2 mL, 20.0 mmol) under nitrogen at room temperature, stirred for 2 h at room temperature and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (silica gel, EtOAc/hexane: 20/80) to give the title compound as a white solid, 1.5 g, mp 40-41°C, identified by NMR and mass spectral analyses.

EXAMPLE 2

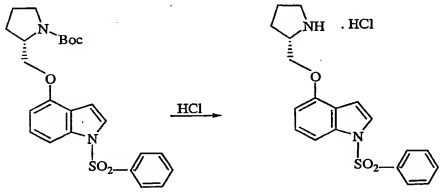
Preparation of t-Butyl (2S)-2-({[1-(phenylsulfonyl)-1H-indol-4-yl]oxy}methyl)-1-pyrrolidinecarboxylate



A stirred solution of t-butyl (2S)-2-[(1H-indol-4-yloxy)methyl]-1-pyrrolidinecarboxylate (1.23 g, 3.89 mmol) in THF is treated with sodium hydride (0.17 g, 60% in mineral oil, 4.28 mmol) under nitrogen at room temperature, stirred for 30 minutes, treated with benzenesulfonyl chloride (0.55 mL, 4.28 mmol), stirred at room temperature for 22 h, quenched with ice-water and diluted with EtOAc. The organic phase is separated, washed sequentially with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is purified by flash chromatography (siliga gel, EtOAc/hexanes, 2/8) to afford the title compound as an off-white foam, 1.21 g, mp 48-50°C, identified by NMR and mass spectral analyses.

EXAMPLE 3

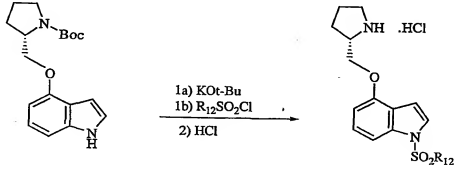
Preparation of 1-(Phenylsulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole hydrochloride



A solution of t-butyl (2S)-2-({[1-phenylsulfonyl)-1H-indol-4-yl]oxy}methyl)-1-pyrrolidinecarboxylate (1.06 g, 2.32 mmol) in methanol and HCl (11.6 mL 1M in ether) is heated at 60°C under nitrogen for 2h, cooled to room temperature and concentrated *in vacuo*. The resultant residue is treated with EtOAc and filtered. The filtercake is dried *in vacuo* to give the title compound as an off-white solid, 0.89 g, mp 194-196°C, identified by NMR and mass spectral analyses.

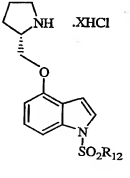
EXAMPLES 4-9

Preparation of 1-(Arylsulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole Hydrochloride



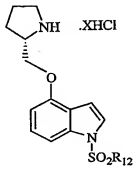
Using essentially the same procedure described in Examples 2 and 3 hereinabove and employing potassium t-butoxide and the appropriate arylsulfonyl chloride, the compounds shown in Table I are obtained and identified by NMR and mass spectral analyses.

Table I



Example No.	R_{12}	X	mp °C
4	5-chlorothien-2-yl	1	204-206
5	2-fluorophenyl	1	153-155

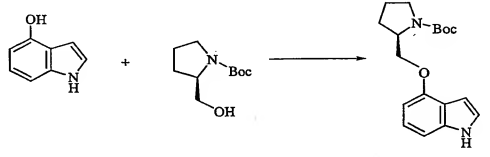
Table I (cont'd)



Example No.	R_{12}	X	mp °C
6	3-fluorophenyl	1	160-162
7	4-fluorophenyl	1	258(dec)
8	3,4-dimethoxyphenyl	1	115(dec)
9	4-aminophenyl	2	150(dec)

EXAMPLE 10

Preparation of t-Butyl (2R)-2-[(1H-indol-4-yloxy)methyl]-pyrrolidine-1-carboxylate

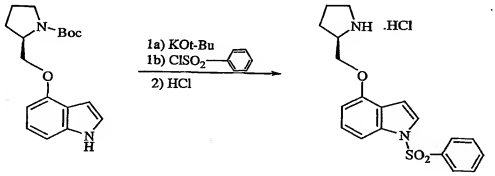


A stirred solution of 4-hydroxyindole (1.33 g, 10.0 mmol), (R)-(+)-1-(t-butoxycarbonyl)-2-pyrrolidinemethanol (4.02 g, 20.0 mmol) and triphenylphosphine (5.3 g, 20.0 mmol) in THF is treated with diethyl azodicarboxylate (3.2 mL, 20 mmol), stirred for 3 h at room temperature

and concentrated *in vacuo*. The resultant residue is treated with EtOAc and filtered through a pad of silica gel. The filtrate is concentrated to give a residue which is purified by chromatography (silica gel, EtOAc:hexanes, 15:80) to afford the title compound as a white solid, 1.08 g, mp 146-147°C; identified by NMR and mass spectral analyses.

EXAMPLE 11

Preparation of 1-(Phenylsulfonyl)-4-[(2R)-pyrrolidin-2-ylmethoxyl-1H-indole hydrochloride

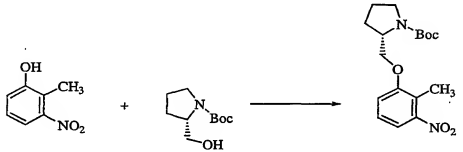


A solution of t-butyl (2R)-2-[(1H-indol-4-yloxy)methyl]pyrrolidine-1-carboxylate (0.316 g, 1.0 mmol) in THF is treated with potassium t-butoxide (1.5 mL, 1.5 mmol, 1M in THF) at room temperature, stirred for 3 min, treated with benzenesulfonyl chloride (0.264 g, 1.5 mmol), stirred for 6 h under nitrogen at room temperature, quenched with 1N aqueous HCl and water and diluted with EtOAc. The organic phase is separated, washed sequentially with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resultant residue is treated with HCl (1.5 mL, 1N in Et_2O), heated at reflux temperature for 3 h, cooled to room temperature and filtered. The filtercake is air-dried to afford the

title compound as an off-white solid, 0.24 g, mp 204-206°C, identified by NMR and mass spectral analyses.

EXAMPLE 12

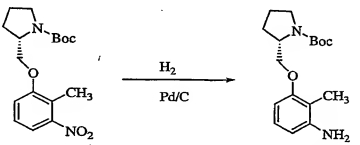
Preparation of t-Butyl (2S)-2-[(2-methyl-3-nitrophenoxy)methyl]pyrrolidine-1-carboxylate



A stirred solution of 2-methyl-3-nitrophenol (3.80 g, 24.84 mmol), (S)-(-)-1-tert-butoxycarbonyl)-2-pyrrolidinemethanol (5.0 g, 24.8 mmol) and triphenylphosphine (6.5 g, 24.8 mmol) in THF is treated with diethylazodicarboxylate (4.3 g, 24.8 mmol), stirred for 3 h at room temperature and concentrated *in vacuo*. The resultant residue is mixed with ether, stored at 0°C overnight and filtered. The filtrate is concentrated *in vacuo* to give a residue which is purified by chromatography (silica gel, EtOAc:hexanes, 20:80) to afford the title compound as a light yellow semisolid, 7.73 g, (91% yield), identified by NMR and mass spectral analyses.

EXAMPLE 13

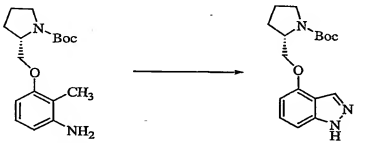
Preparation of t-Butyl (2S)-2-[(3-amino-2-methylphenoxy)methyl]pyrrolidine-1-carboxylate



A solution of t-butyl (2S)-2-[(2-methyl-3-nitrophenoxy)methyl]pyrrolidine-1-carboxylate (7.63 g, 21.9 mmol) and 10% Pd/C (0.38 g) in ethanol is hydrogenated (50 psi) at room temperature for 4 h and filtered. The filtrate is concentrated *in vacuo* to afford the title compound as an off-white solid, 6.66 g, mp 110°C, identified by NMR and mass spectral analyses.

EXAMPLE 14

Preparation of t-Butyl (2S)-2-[(1H-indazol-4-yloxy)methyl]pyrrolidine-1-carboxylate

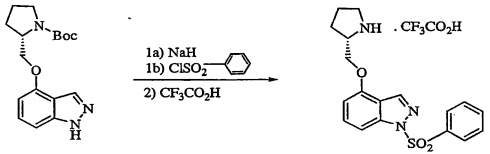


A solution of t-butyl (2S)-2-[(3-amino-2-methylphenoxy) methyl]pyrrolidine-1-carboxylate (5.00 g, 16.33 mmol), potassium acetate (1.92 g, 19.6 mmol) and acetic anhydride (4.9 mL, 52.3 mmol) in benzene is treated dropwise with isoamylnitrite (4.3 mL, 32.7 mmol),

heated at reflux temperature overnight, cooled to room temperature and filtered. The filtercake is washed with benzene. The filtrates are combined and concentrated *in vacuo* to give a yellow oil residue. The residue is purified by chromatography (silica gel, EtOAc:hexanes, 15:85). The purified oil (5.05 g) is dissolved in ethanol, treated with 40% aqueous NaOH, heated at reflux temperature for 45 min, cooled in an ice-water bath, neutralized to pH 8 with concentrated HCl and concentrated *in vacuo* to remove the ethanol. The resultant aqueous residue is extracted with EtOAc. The combined extracts are washed sequentially with water and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. This oil is purified by chromatography (silica gel, EtOAc:hexanes, 30:70) to give the title product as an off-white solid, 3.52 g, mp 125°C, identified by NMR and mass spectral analyses.

EXAMPLE 15

Preparation of 1-(Phenylsulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazole trifluoroacetic acid salt

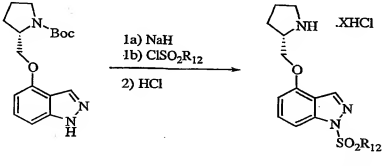


A solution of t-butyl (2S)-2-[(1H-indazol-4-yloxy)methyl]pyrrolidine-1-carboxylate (0.317 g, 1.0 mmol) in dimethylformamide is treated with sodium hydride (0.08 g, 2.0 mmol, 60% in mineral oil) at room temperature, stirred for 10 min, treated with

benzenesulfonyl chloride (0.264 g, 1.5 mmol), stirred for 18 h under nitrogen at room temperature, quenched with water and diluted with ether. The organic phase is separated, washed sequentially with water and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a white foam residue. The residue is purified by chromatography (silica gel, EtOAc:hexanes, 15:85) to give a white solid. This solid is dissolved in trifluoroacetic acid at 0°C, stirred at room temperature for 90 min and concentrated *in vacuo*. The resultant residue is triturated under ether to afford the title compound as a white solid, 300 mg, mp 218-219°C, identified by NMR and mass spectral analyses.

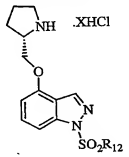
EXAMPLES 16-21

Preparation of 1-Arylsulfonyl-4[(2S)-pyrrolidinylmethoxy]1H-indazole Hydrochloride



Using essentially the same procedure described in Example 15 hereinabove and employing the appropriate arysulfonyl chloride and anhydrous HCl, the compounds in Table II are obtained and identified by NMR and mass spectral analyses.

Table II



Example No.	R_{12}	X	mp °C
16	8-quinolinyl	0	217-218
17	2-chlorophenyl	1	>255(dec)
18	2-fluorophenyl	1	145-148
19	5-chlorothien-2-yl	1	195
20	4-aminophenyl	2	150-155
21	4-amino-3-chlorophenyl	2	220(dec)

EXAMPLE 22

Comparative Evaluation of 5-HT6 Binding Affinity of Test Compounds

The affinity of test compounds for the serotonin 5-HT6 receptor is evaluated in the following manner. Cultured Hela cells expressing human cloned 5-HT6 receptors are harvested and centrifuged at low speed (1,000 x g) for 10.0 min to remove the culture media. The harvested cells are suspended in half volume of fresh physiological phosphate buffered saline solution and recentrifuged at the same speed. This operation is

repeated. The collected cells are then homogenized in ten volumes of 50 mM Tris.HCl (pH 7.4) and 0.5 mM EDTA. The homogenate is centrifuged at 40,000 x g for 30.0 min and the precipitate is collected. The obtained pellet is resuspended in 10 volumes of Tris.HCl buffer and recentrifuged at the same speed. The final pellet is suspended in a small volume of Tris.HCl buffer and the tissue protein content is determined in aliquots of 10-25 µl volumes. Bovine Serum Albumin is used as the standard in the protein determination according to the method described in Lowry et al., J. Biol. Chem., 193:265 (1951). The volume of the suspended cell membranes is adjusted to give a tissue protein concentration of 1.0 mg/ml of suspension. The prepared membrane suspension (10 times concentrated) is aliquoted in 1.0 ml volumes and stored at -70° C until used in subsequent binding experiments.

Binding experiments are performed in a 96 well microtiter plate format, in a total volume of 200 µl. To each well is added the following mixture: 80.0 µl of incubation buffer made in 50 mM Tris.HCl buffer (pH 7.4) containing 10.0 mM $MgCl_2$ and 0.5 mM EDTA and 20 µl of [^{3}H]-LSD (S.A., 86.0 Ci/mmol, available from Amersham Life Science), 3.0 nM. The dissociation constant, K_b of the [^{3}H]LSD at the human serotonin 5-HT6 receptor is 2.9 nM, as determined by saturation binding with increasing concentrations of [^{3}H]LSD. The reaction is initiated by the final addition of 100.0 µl of tissue suspension. Nonspecific binding is measured in the presence of 10.0 µM methiothepin. The test compounds are added in 20.0 µl volume.

The reaction is allowed to proceed in the dark for 120 min at room temperature, at which time, the bound ligand-receptor complex is filtered off on a 96 well unifilter with a Packard Filtermate® 196 Harvester. The

bound complex caught on the filter disk is allowed to air dry and the radioactivity is measured in a Packard TopCount® equipped with six photomultiplier detectors, after the addition of 40.0µl Microscint®-20 scintillant to each shallow well. The unifilter plate is heat-sealed and counted in a PackardTopCount® with a tritium efficiency of 31.0%.

Specific binding to the 5-HT6 receptor is defined as the total radioactivity bound less the amount bound in the presence of 10.0µM unlabeled methiothepin. Binding in the presence of varying concentrations of test compound is expressed as a percentage of specific binding in the absence of test compound. The results are plotted as log % bound versus log concentration of test compound. Nonlinear regression analysis of data points with a computer assisted program Prism® yielded both the IC_{50} and the K_i values of test compounds with 95% confidence limits. A linear regression line of data points is plotted, from which the IC_{50} value is determined and the K_i value is determined based upon the following equation:

$$K_i = IC_{50} / (1 + L/K_D)$$

where L is the concentration of the radioactive ligand used and K_D is the dissociation constant of the ligand for the receptor, both expressed in nM.

Using this assay, the following Ki values are determined and compared to those values obtained by representative compounds known to demonstrate binding to the 5-HT6 receptor. The data are shown in Table III, below.

Table III

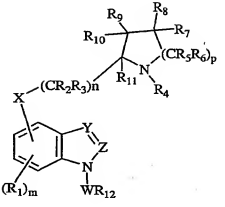
Test Compound (Ex. No.)	5-HT6 Binding Ki (nM)
3	6.0
4	7.0
5	2.0
6	8.0
7	31.0
8	95.0
9	1.0
11	106
15	7.0
16	85.0
17	5.0
18	8.0
19	5.0
20	9.0
21	16.0

Comparative Examples	5-HT6 Binding Ki (nM)
Clozapine	6.0
Loxapine	41.4
Bromocriptine	23.0
Methiothepin	8.3
Mianserin	44.2
Olanzepine	19.5

As can be seen from the results set forth above, the compounds of the present invention have a high degree of affinity for the 5-HT6 receptor.

WHAT IS CLAIMED IS:

1. A compound of formula I



(I)

wherein

W is SO_2, CO, CONH, CSNH or $(CH_2)_x$;

X is O, SO_y or NR_{13};

Y is CR_{14} or N;

Z is CR_{15} or N with the proviso that when Y is N then Z must be CR_{15};

m and x are each independently 0 or an integer of 1, 2 or 3;

n and p are each independently an integer of 1, 2 or 3;

R_1 is halogen, CN, OR_{16}, CO_2R_{17}, $CONR_{18}R_{19}$, $CNR_{20}NR_{21}R_{22}$, $SO_2NR_{23}R_{24}$, SO_wR_{25}, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_4 is H, $CNR_{26}NR_{27}R_{28}$ or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{12} is an optionally substituted C_1-C_6alkyl, aryl or heteroaryl group;

y and w are each 0 or an integer of 1 or 2;

R_{13} is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{14} and R_{15} are each independently H, halogen or a C_1-C_6alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_{16} is H, COR_{29} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{17} and R_{29} are each independently H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26}, R_{27} and R_{28} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{23} and R_{24} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{25} is an optionally substituted C_1-C_6alkyl, aryl, or heteroaryl group; or

a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein W is SO_2.

3. A compound according to claim 1 or claim 2 wherein X is O.

4. A compound according to any one of claims 1 to 3 wherein Y is CR_{14}.

5. A compound according to any one of claims 1 to 4 wherein n is 1.

6. A compound according to any one of claims 1 to 5 wherein R_{12} is an aryl or heteroaryl group each optionally substituted.

7. A compound according to any one of claims 1 to 6 wherein R_2 and R_3 are both H.

8. A compound according to any one of claims 1 to 7 wherein p is 1.

9. A compound according to claim 1 selected from the group consisting of:
1-(phenylsulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;
1-[(5-chlorothien-2-yl)sulfonyl]-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;
1-[(2-fluorophenyl)sulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;
1-[(3-fluorophenyl)sulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;
1-[(4-fluorophenyl)sulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;
1-[(3,4-dimethoxyphenyl)sulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indole;
4-({4-[2S)-pyrrolidin-2-ylmethoxy]-1H-indole-1-yl}sulfonyl)aniline;

1-(phenylsulfonyl)-4-[(2R)-pyrrolidin-2-ylmethoxy]-1H-indole;

1-(phenylsulfonyl)-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazole;

8-({4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazol-1-yl}sulfonyl)quinoline;

1-[(2-chlorophenyl)sulfonyl]-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazole;

1-[(2-fluorophenyl)sulfonyl]-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazole;

1-[(5-chlorothien-2-yl)sulfonyl]-4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazole;

4-({4-[(2S)-pyrrolidin-2-ylmethoxy}-1H-indazol-1-yl}sulfonyl)aniline;

2-chloro-4-({4-[(2S)-pyrrolidin-2-ylmethoxy]-1H-indazol-1-yl}sulfonyl)aniline;

1-(phenylsulfonyl)-4-(piperidin-2-ylmethoxy)-1H-indole;

4-{[4-(piperidin-2-ylmethoxy)-1H-indol-1-yl]sulfonyl}aniline;

1-[(2-fluorophenyl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indole;

1-[(5-chlorothien-2-yl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indole;

1-[(3-fluorophenyl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indole;

1-[(2-fluorophenyl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indazole;

1-[(2-chlorophenyl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indazole;

1-[(5-chlorothien-2-yl)sulfonyl]-4-(piperidin-2-ylmethoxy)-1H-indazole;

4-(azepan-2-ylmethoxy)-1-(phenylsulfonyl)-1H-indole;

4-{[4-(azepan-2-ylmethoxy)-1H-indol-1-yl]sulfonyl}aniline;

4-(azepan-2-ylmethoxy)-1-[(2-fluorophenyl)sulfonyl]-1H-indole;
4-(azepan-2-ylmethoxy)-1-[(5-chlorothien-2-yl)sulfonyl]-1H-indole;
4-(azepan-2-ylmethoxy)-1-[(3-fluorophenyl)sulfonyl]-1H-indole;
4-(azepan-2-ylmethoxy)-1-[(2-fluorophenyl)sulfonyl]-1H-indazole;
4-(azepan-2-ylmethoxy)-1-[(2-chlorophenyl)sulfonyl]-1H-indazole;
4-(azepan-2-ylmethoxy)-1-[(5-chlorothien-2-yl)sulfonyl]-1H-indazole;
1-(phenylsulfonyl)-5-(pyrrolidin-2-ylmethoxy)-1H-indole;
1-(phenylsulfonyl)-6-(pyrrolidin-2-ylmethoxy)-1H-indole;
1-(phenylsulfonyl)-5-(pyrrolidin-2-ylmethoxy)-1H-indazole;
1-(phenylsulfonyl)-6-(pyrrolidin-2-ylmethoxy)-1H-indazole; or a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

10. A method for the treatment of a disorder of the central nervous system related to or affected by the 5-HT6 receptor in a patient in need thereof which comprises providing to said patient a therapeutically effective amount of a compound of formula I as claimed in any one of claims 1 to 9 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

11. The method according to claim 10 wherein said disorder is a motor disorder, anxiety disorder or cognitive disorder.

12. The method according to claim 10 wherein said disorder is schizophrenia or depression.

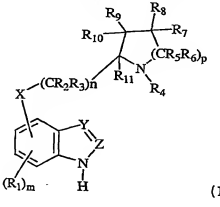
13. The method according to claim 11 wherein said disorder is Alzheimer's disease or Parkinson's diease.

14. The method according to claim 11 wherein said disorder is attention deficit disorder.

15. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and a compound of formula I as claimed in any one of claims 1 to 9 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof.

16. A process for the preparation of a compound of formula I which comprises one of the following:

b) reacting a compound of formula (B):



(B)

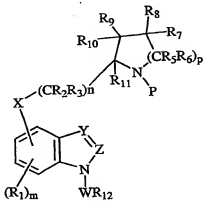
wherein m, n, p, X, Y, Z, R_1, R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are as defined herein, with an appropriate sulphonylating, acylating, carbamoylating, thiocarbamoylating, arylating or alkylating agent containing the group:

R_{12}-W-

where R_{12} is as defined above and W is SO_2, CO, CONH, CSNH or $(CH_2)_x$; said reactants protected on reactive sites and/or on reactive substituent groups as required, and removing any protecting groups, to give a corresponding compound of formula (I);

or

b) removing a protecting group from a compound of formula (C)



(I) (C)

wherein m, n, p, W, X, Y, Z, R_1, R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are as defined herein and P is a protecting group to give a compound of formula (I) wherein R_4 is H;

or

c) alkylating a compound of formula (I) as defined in claim 1 wherein R_4 is hydrogen with an alkylating agent of formula R_4-L wherein L is a leaving group, such as halogen, and R_4 is as defined in claim 1 excepting hydrogen to give a corresponding compound of formula (I);

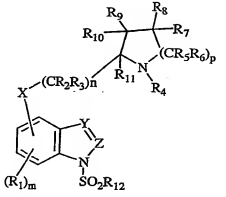
or

d) converting a compound of formula (I) having a reactive substituent group to a different compound of formula I;

or

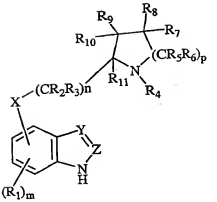
e) converting a basic compound of formula (I) to an acid addition salt or vice versa.

17. A process for the preparation of a compound of formula Ie



(Ie)

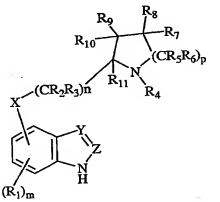
wherein X, Y, Z, m, n, p, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are as defined in claim 1 which comprises reacting a compound of formula XVI



(XVI)

wherein X, Y, Z, m, n, p, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are as defined hereinabove with a sulfonyl chloride, $R_{12}SO_2Cl$, wherein R_{12} is as defined hereinabove in the presence of a base optionally in the presence of a solvent.

18. A compound of formula XVI



(XVI)

wherein

X is O, SO_y or NR_{13};

Y is CR_{14} or N;

Z is CR_{15} or N with the proviso that when Y is N then Z must be CR_{15};

m is 0 or an integer of 1, 2 or 3;

n and p are each independently an integer of 1, 2 or 3;

R_1 is halogen, CN, OR_{16}, CO_2R_{17}, $CONR_{18}R_{19}$, $CNR_{20}NR_{21}R_{22}$, $SO_2NR_{23}R_{24}$, SO_wR_{25}, or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, phenyl or heteroaryl group each optionally substituted;

R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_{10} and R_{11} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_4 is H, $CNR_{26}NR_{27}R_{28}$ or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl or cycloheteroalkyl group each optionally substituted;

R_{13} is H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{14} and R_{15} are each independently H, halogen or a C_1-C_6alkyl, aryl, heteroaryl or C_1-C_6alkoxy group each optionally substituted;

R_{16} is H, COR_{29} or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, aryl or heteroaryl group each optionally substituted;

R_{17} and R_{29} are each independently H or a C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group each optionally substituted;

R_{18}, R_{19}, R_{20}, R_{21}, R_{22}, R_{26}, R_{27} and R_{28} are each independently H or an optionally substituted C_1-C_6alkyl group;

R_{23} and R_{24} are each independently H or a C_1-C_6alkyl, aryl or heteroaryl group each optionally substituted; and

R_{25} is an optionally substituted C_1-C_6alkyl, aryl, or heteroaryl group; or

the stereoisomers thereof or the pharmaceutically acceptable salts thereof.

19. A compound according to claim 18 wherein X is O; Y is CR_{14}; and n is 1.

20. A compound according to claim 18 or claim 19 wherein Z is CR_{15}.

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(71) Applicant: WYETH [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).

(72) Inventors: LI, Yanfang; 3 Woodlane Road, Lawrenceville, NJ 08648 (US). ZHOU, Ping; 28 Marion Drive, Plainsboro, NJ 08536 (US).

(74) Agents: BERG, Egon, E.; Wyeth, Patent Law Department, Five Giralda Farms, Madison, NJ 07940 et al. (US).

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Published:
— *with international search report*
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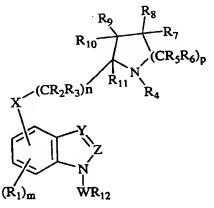
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROCYCLYLALKOXY-, -ALKYLTHIO- AND -ALKYLAMINOBENZAZOLE DERIVATIVES AS 5-HYDROXYTRYPTAMINE-6 LIGANDS



(I)

(57) Abstract: The present invention provides a compound of formula I and the use thereof for the therapeutic treatment of disorders relating to or affected by the 5-HT6 receptor.

WO 02/085853 A3

INTERNATIONAL SEARCH REPORT

Interna[illegible]al Application No
PCT/US 02/12512

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D403/12 A61K31/44 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 03298 A (FUJISAWA PHARMACEUTICAL CO ;SAWADA KOZO (JP); YATABE TAKUMI (JP);) 2 February 1995 (1995-02-02) claim 1	1-9, 15-20
Y	US 6 054 469 A (SHOWELL GRAHAM ANDREW ET AL) 25 April 2000 (2000-04-25) claim 1	1-9, 15-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance
E earlier document but published on or after the international filing date
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O document referring to an oral disclosure, use, exhibition or other means
P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
& document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 October 2002	17/10/2002

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Wolf, C

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 10-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 10-14

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 02/12512

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10-14
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna[illegible]al Application No
PCT/US 02/12512

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9503298	A	02-02-1995	AU	7195694 A	20-02-1995
			WO	9503298 A1	02-02-1995
			JP	9505029 T	20-05-1997
US 6054469	A	25-04-2000	AU	7578396 A	05-06-1997
			WO	9718204 A1	22-05-1997

Form PCT/ISA/210 (patent family annex) (July 1992)